

CLAIMS

1. An anhydrous form of sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide (Anhydrous Form B)
5 having an X-ray powder diffraction pattern containing specific peaks at: 3.8 ($\pm 0.1^\circ$), 7.5 ($\pm 0.1^\circ$), 11.2 ($\pm 0.1^\circ$), 13.0 ($\pm 0.1^\circ$), 13.8 ($\pm 0.1^\circ$), 15.0 ($\pm 0.1^\circ$), 15.7 ($\pm 0.1^\circ$), 18.8 ($\pm 0.1^\circ$), 20.2 ($\pm 0.1^\circ$), 21.7 ($\pm 0.1^\circ$), 22.6 ($\pm 0.1^\circ$) and 30.2 ($\pm 0.1^\circ$) 2 θ .
2. An anhydrous form of sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide (Anhydrous Form C)
10 having an X-ray powder diffraction pattern containing specific peaks at: 4.3 ($\pm 0.1^\circ$), 8.5 ($\pm 0.1^\circ$), 14.6 ($\pm 0.1^\circ$), 15.3 ($\pm 0.1^\circ$), 16.1 ($\pm 0.1^\circ$), 17.4 ($\pm 0.1^\circ$), 18.7 ($\pm 0.1^\circ$), 20.5 ($\pm 0.1^\circ$), 22.1 ($\pm 0.1^\circ$), 22.6 ($\pm 0.1^\circ$), 23.1 ($\pm 0.1^\circ$) and 29.6 ($\pm 0.1^\circ$) 2 θ .
3. A hydrated form of sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide (Hydrate Form A) having an X-ray powder diffraction pattern containing specific peaks at: 4.2 ($\pm 0.1^\circ$), 8.2 ($\pm 0.1^\circ$), 8.5 ($\pm 0.1^\circ$), 9.1 ($\pm 0.1^\circ$), 11.5 ($\pm 0.1^\circ$), 12.7 ($\pm 0.1^\circ$), 14.8 ($\pm 0.1^\circ$), 15.4 ($\pm 0.1^\circ$), 16.6 ($\pm 0.1^\circ$), 17.4 ($\pm 0.1^\circ$), 17.7 ($\pm 0.1^\circ$), 18.2 ($\pm 0.1^\circ$), 20.4 ($\pm 0.1^\circ$), 23.2 ($\pm 0.1^\circ$), 29.1 ($\pm 0.1^\circ$) and 29.8 ($\pm 0.1^\circ$) 2 θ .
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4. A compound as claimed in claim 3 wherein the water of crystallisation is 3-10% w/w.
5. A hydrated form of sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide (Hydrate Form B) having an X-ray powder diffraction pattern containing specific peaks at: 4.5 ($\pm 0.1^\circ$), 7.3 ($\pm 0.1^\circ$), 8.3 ($\pm 0.1^\circ$), 13.3 ($\pm 0.1^\circ$), 14.5 ($\pm 0.1^\circ$), 14.8 ($\pm 0.1^\circ$), 15.4 ($\pm 0.1^\circ$), 16.6 ($\pm 0.1^\circ$), 18.7 ($\pm 0.1^\circ$), 20.2 ($\pm 0.1^\circ$), 21.1 ($\pm 0.1^\circ$), 21.5 ($\pm 0.1^\circ$), 21.9 ($\pm 0.1^\circ$), 22.3 ($\pm 0.1^\circ$), 23.5 ($\pm 0.1^\circ$) and 24.9 ($\pm 0.1^\circ$) 2 θ .
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6. A compound as claimed in claim 5 wherein the water of crystallisation is 5-7% w/w.

7. A hydrated form of the sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide (Hydrate Form C) having an X-ray powder diffraction pattern containing specific peaks at: 4.2 (±0.1°), 7.5 (±0.1°), 8.0 (±0.1°), 11.4 (±0.1°), 12.5 (±0.1°), 15.1 (±0.1°), 15.8 (±0.1°), 17.7 (±0.1°), 18.9 (±0.1°), 20.5 (±0.1°), 21.1 (±0.1°), 22.7 (±0.1°), 24.6 (±0.1°), 26.1 (±0.1°), 27.8 (±0.1°) and 29.2 (±0.1°) 2θ.

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8. A compound as claimed in claim 7 wherein the water of crystallisation is 3-10% w/w.

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9. A hydrated form of the sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide (Hydrate Form D) having an X-ray powder diffraction pattern containing specific peaks at: 8.8 (±0.1°), 10.5 (±0.1°), 11.8 (±0.1°), 12.9 (±0.1°), 15.6 (±0.1°), 17.1 (±0.1°), 18.9 (±0.1°), 20.8 (±0.1°), 23.3 (±0.1°), 25.6 (±0.1°), 26.1 (±0.1°), 26.9 (±0.1°), 28.1 (±0.1°), 30.6 (±0.1°), 32.5 (±0.1°) and 33.1 (±0.1°) 2θ.

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10. A solvated form of the sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide (Solvated Form E) having an X-ray powder diffraction pattern containing specific peaks at: 3.6 (±0.1°), 7.1 (±0.1°), 8.3 (±0.1°), 9.3 (±0.1°), 9.8 (±0.1°), 14.1 (±0.1°), 15.9 (±0.1°), 17.7 (±0.1°), 18.6 (±0.1°), 19.3 (±0.1°), 21.7 (±0.1°), 23.1 (±0.1°), 24.1 (±0.1°), 25.0 (±0.1°), 25.8 (±0.1°) and 26.3 (±0.1°) 2θ.

11. A crystalline form of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide (Form A) having an X-ray powder diffraction pattern containing specific peaks at: 7.3 (±0.1°), 8.5 (±0.1°), 10.6 (±0.1°), 13.4 (±0.1°), 14.7 (±0.1°), 15.4 (±0.1°), 15.9 (±0.1°), 19.9 (±0.1°), 20.2 (±0.1°), 21.7 (±0.1°), 25.8 (±0.1°) and 26.6 (±0.1°) 2θ.

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12. A crystalline form of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide (Form B) having an X-ray powder diffraction pattern

containing specific peaks at: 9.9 ($\pm 0.1^\circ$), 10.5 ($\pm 0.1^\circ$), 11.0 ($\pm 0.1^\circ$), 11.6 ($\pm 0.1^\circ$), 13.3 ($\pm 0.1^\circ$), 13.9 ($\pm 0.1^\circ$), 14.9 ($\pm 0.1^\circ$), 18.0 ($\pm 0.1^\circ$), 19.0 ($\pm 0.1^\circ$), 20.4 ($\pm 0.1^\circ$), 22.2 ($\pm 0.1^\circ$) and 23.0 ($\pm 0.1^\circ$) 20.

5 13. A pharmaceutical composition comprising a compound as claimed in claims 1 to 12 and a pharmaceutically acceptable adjuvant, diluent or carrier.

10 14. A compound as claimed in claims 1 to 12 for use in therapy.

15 15. The use of a compound as claimed in claims 1 to 12 in the manufacture of a medicament for use in therapy.

15 16. A method of treating a chemokine mediated disease state in a mammal suffering from, or at risk of, said disease, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound as claimed in claims 1 to 12.

20 17. A process for preparing Anhydrous Form B comprising:

- drying a water-wet or hydrated form of a sample of the sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methylbenzenesulfonamide in the presence of phosphorus pentoxide under reduced pressure; or,
- heating a sample of Hydrate Form A from ambient temperature to 100°C.

25 18. A process for preparing Anhydrous Form C comprising heating a sample of Hydrate Form B from ambient temperature to 100°C.

30 19. A process for preparing Hydrate Form A comprising reacting 4-(3,4-dichlorophenoxy)-1,4'-bipiperidine with 4-methylbenzenesulfonyl isocyanate in a suitable solvent at ambient temperature to form *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methylbenzenesulfonamide in the suitable solvent; adding to that concentrated aqueous sodium hydroxide solution followed by water; and:

- a. stirring the resulting mixture to allow the sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methylbenzenesulfonamide, possibly contaminated with suitable solvent, to precipitate out with Hydrate Form A remaining after filtration and drying,
5 or,
b. distilling the suitable solvent and allowing Hydrate Form A to precipitate from the aqueous.

20. A process for preparing Hydrate Form A comprising adding concentrated aqueous
10 sodium hydroxide solution to a mixture of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methylbenzenesulfonamide in water at a temperature in the range 30-60°C and allowing the mixture to cool with the sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methylbenzenesulfonamide precipitating and Hydrate Form A remaining after filtering and
15 drying.

21. A process for preparing Hydrate Form A as claimed in claim 20 comprising:

- a. mixing *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methylbenzenesulfonamide with water and heating the mixture to a temperature in the range 30-60°C; and,
20 b. adding concentrated aqueous sodium hydroxide solution and allowing the mixture to cool with the sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methylbenzenesulfonamide precipitating and Hydrate Form A remaining after filtering and drying.

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22. A process for preparing Hydrate Form A comprising adding concentrated aqueous sodium hydroxide solution to *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methylbenzenesulfonamide in a suitable organic solvent; heating the mixture and separating the aqueous layer; adding IMS and, optionally, toluene to the aqueous phase and cooling the resulting mixture; and, filtering off and drying the solid that forms.
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23. A process for preparing Hydrate Form A comprising heating a mixture of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methylbenzenesulfonamide (Form B) and aqueous sodium hydroxide; cooling the mixture and extracting the cooled mixture with dichloromethane; combining the extracts; 5 optionally reducing the volume of the combined organic extracts; cooling the dichloromethane mixture so that the sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide precipitates; and, filtering off and drying the solid that forms.

10 24. A process for preparing Hydrate Form A comprising drying a sample of Hydrate Form D under reduced pressure at a temperature in the range 10-100°C.

25. A process for preparing Hydrate Form A comprising drying a sample of Solvated Form E at atmospheric pressure at a temperature in the range 0-30°C.

15 26. A process for preparing Hydrate Form B comprising mixing a solution of 4-(3,4-dichlorophenoxy)-1,4'-bipiperidine in tetrahydrofuran with a solution of 4-methylbenzenesulfonyl isocyanate in tetrahydrofuran at a temperature in the range 15-35°C; adding aqueous sodium hydroxide solution and collecting the solid that 20 precipitates.

27. A process for preparing Hydrate Form C comprising cooling a solution of the sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide in a mixture of water and acetone from reflux to around 0°C and collecting the solid product that forms.

25 28. A process for preparing Hydrate Form C comprising drying a sample of Solvated Form E reduced pressure at a temperature in the range 10-100°C.

30 29. A process for preparing Hydrate Form D comprising cooling a solution of the sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide in a mixture of water and 2-propanol from 50-80°C to 0-10°C and filtering off the residue.

30. A process for preparing Solvated Form E comprising cooling a solution of the sodium salt of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide in a mixture of water, IMS and toluene from 50-80°C to 0-10°C and filtering off the residue.

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31. A process for preparing *N*-[[4-(3,4-Dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide (Form A) comprising:

10 a. purifying *N*-[[4-(3,4-dichlorophenoxy)-[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide using reverse phase chromatography eluting with a mixture of aqueous ammonia and acetonitrile; and,

15 b. freeze drying the fractions containing *N*-[[4-(3,4-dichlorophenoxy)-[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide and triturating the residue with acetonitrile and then drying the residue under reduced pressure at ambient temperature.

32. A process for preparing *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide (Form A) comprising:

20 a. heating a mixture of *N*-[[4-(3,4-dichlorophenoxy)[1,4'-bipiperidin]-1'-yl]carbonyl]-4-methyl-benzenesulfonamide Form B and acetonitrile to 40-60°C; and,

25 b. drying the solid from the slurry so formed under reduced pressure.